

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/033698

International filing date (day/month/year)
14.10.2004

Priority date (day/month/year)
16.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07C279/28, C07C237/22, A61K31/17, A61K31/165, A61P25/04

Applicant
FERRING B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 17 for industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 17 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-8(part), 10-12(part), 14-17(part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	9, 13
	No: Claims	1-8, 10-12, 14-17
Inventive step (IS)	Yes: Claims	1-8, 10-17
	No: Claims	9
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	

2. Citations and explanations

see separate sheet

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IP20 Rec'd PCT/PTO 13 APR 2006
International application No.

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Reference is made to the following documents:

- D1 DE 33 29 628 A1
- D2 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 8702792
- D3 DE 20 05 326 A1
- D4 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 2808453
- D5 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 2993980
- D6 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 7033473
- D7 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 4450540, 4435773
- D8 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 7218655, 7218660
- D9 US-A-5 516 795
- D10 US-A-2 447 587
- D11 DATABASE BEILSTEIN, BEILSTEIN INSTITUT ZUR FÖRDERUNG DER
CHEMISCHEN WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; Database
accession no. BRN 2669014
- D12 J. ORG. CHEM., vol. 58, no. 6, 1993, pages 1425-1433

**III. Non-establishment of opinion with regard to novelty, inventive step and
industrial applicability**

Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds of formula (I) whereby Z has the values of claim 6. Despite this limitation the search still revealed too many relevant documents for the issue of novelty. Therefore the search has been further restricted to compounds of formula (I) whereby Z is equal to $(CH_2)_3$ or to 1,2-cycloalkylene, which includes all explicitly mentioned compounds.

V. Reasoned statement with regard to novelty, inventive step or industrial applicability

Novelty

The present application refers to compounds of the general formula (I) (claim 1), pharmaceutical compositions comprising them (claim 15) and their use in the treatment of pain (claims 16 and 17).

Compounds falling within the scope of claim 1 and the dependent claims 2-8 and 10-12 are anticipated by the documents D1-D12 (see the cited passages in the International search report). Claims 1-8 and 10-12 are therefore not considered to meet the requirement of Art. 33(2) PCT.

Document D1, furthermore, discloses a pharmaceutical use for compounds according to claim 1, pharmaceutical compositions comprising them and their use as analgetica (see D1, abstract; claims 18-20; page 67, line 13). The subject-matter of claims 14-17

is therefore not considered to be novel contrary to the requirement of Art. 33(2) PCT. It should be noted that D1 not only anticipates explicit compounds falling within the scope of formula (I), but the compounds according to D1 overlap with the presently claimed compounds. No novel teaching is present for this overlapping area (Art. 33(2) PCT).

The explicit compounds mentioned in claims 9 and 13 of the present application appear to meet the requirement of Art. 33(2) PCT, because none of the available prior art documents discloses such compounds.

Inventive step

The problem to be solved by the present invention was the provision of further compounds for the treatment of pain.

With regard to D1, which already discloses compounds of formula (I) with $X=CHR^1$ for the same use, no inventive step can be acknowledged for the subject-matter of claims 1, 10-13 and 14-17 (amide derivatives).

With regard to the urea derivatives, i.e. compounds of claim 1 with $X=NR^1$ (claims 1-9, 14-17), no inventive step can be acknowledged for the following reasons: To be considered inventive the technical problem has to be solved over basically the whole scope of the claims. However, claim 1 encompasses a large amount of compounds, while only a very small part is supported by the description (i.e. compounds of formula (I) with Z equal to $(CH_2)_3$ or to 1,2-cycloalkylene). Especially the biological data are insufficient to demonstrate whether the problem is actually solved over basically the whole scope of the claims. Without such data no inventive step can be acknowledged.

This objection, in addition to the aforementioned objection, is also valid for the amide derivatives.

The subject-matter of claim 9 appears to meet the requirement of Art. 33(3) PCT.

It should be noted that with regard to D1 the present application appears to lack unity of invention.

Industrial applicability

For the assessment of the present claim 17 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

There are no objections against the industrial applicability of the subject-matter of claims 1-16.

Further remarks:

The claims are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: The claims encompass a large amount of compounds, while only a very small part is supported by the description (explicit examples). Furthermore, the biological data are not sufficient to support the fact that all compounds falling within the formula (I) have the desired activity.

Claim 12 is unclear (Art. 6 PCT). It is especially unclear whether it has to be understood that Y, Z, Ar, R₂, R₃ and R₆ should assume the values defined in claims 4-8 at the same time or independently (equivalent to separate claims similar to claims 4-8).

It has been understood that the variable Ar can be substituted by the substituents (b) to (l) (see description page 4, line 10-11). This is not reflected in claim 1, where no substitution

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is mentioned for Ar. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

It should be noted that a possible substitution on Ar has been taken into account both in the search and for the purpose of the present opinion.

A bicyclic heteroaromatic ring system generally does not include a ring system whereby one of the rings is a phenyl or a five- or six-membered heteroaromatic ring fused with a heterocyclyl, whereby the heterocyclyl is saturated or partially saturated (see application page 4, line 31 - page 5, line 17). This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT. Specific definitions should be present in the claims. A similar objection is valid with regard to the definition "C₁₋₆ straight alkyl" in the claims. This definition does not include isopropyl or 2-n-butyl groups (see application page 5, lines 18-21).

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.